STUDIES IN THE SYNTHESIS OF ANALOGS OF PTEROYLGLUTAMIC ACID

BY

HAROLD ROSENBERG

B.S., Roosevelt College, 1946
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1950

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STUDIES IN THE SYNTHESIS OF ANALOGS OF PTEROYLGLUTAMIC ACID

Introduction

Experimental results obtained by various investigators in recent years have shown that relatively slight structural changes in many compounds which possess metabolic functions may result in the formation of new compounds which are metabolically antagonistic to those from which they are derived. Such antagonistic analogs are now known for most of the vitamins and for certain hormones, amino acids, porphyrins and purines. The metabolite antagonists (antimetabolites) are of interest as chemotherapeutic agents and have often served as the basic of biochemical investigations.

Since the establishment of its identity (1) and description of its synthesis (1,2) several years ago, the vitamin, pteroylglutamic (folic) acid, has assumed great importance in biochemical studies, particularly in connection with the treatment of pernicious anemia. More recently, however, its antagonistic analogs have been of greater interest as a result of the discovery of their value in leukemia and cancer therapy. The present work was undertaken in an effort to synthesize certain structural analogs of pteroylglutamic acid which might function as antimetabolites and possess potential chemotherapeutic significance.

Discussion of Results

Six new structural analogs of pteroylglutamic acid have been prepared to permit physiological study with reference to their possible action as antivitamins.

N-{ -*p*-[(2,4-Diamino-7,10-dimethyl-6-pteridylmethyl) methylamino]-benzoyl }-glutamic acid was synthesized from 2,4,5,6-tetraaminopyrimidine sulfate, 2,3-dibromobutyraldehyde and *p*-methylaminobenzoylglutamic acid. *p*-[(2,4-Di-

amino-6-pteridylmethyl) methylamino]-benzoic acid was prepared in a similar manner, except that *p*-methylaminobenzoic acid was substituted for *p*-methylaminobenzoylglutamic acid.

N-{-*p*-[(2,4-Dihydroxy-6-pteridylmethyl) methylamino]-benzoyl}-glutamic acid was prepared by two different routes. By one method, 4,5-diamino-2,6-dihydroxypyrimidine sulfate was condensed with 2,3-dibromopropionaldehyde and *p*-methylaminobenzoylglutamic acid to give the analog. The second method consisted of the following sequence: *o*-phenylenediamine, 2-methylquinoxaline, 5-methylpyrazine-2,3-dicarboxylic acid, ethyl 5-methylpyrazine-2,3-dicarboxylate, 5-methylpyrazine-2,3-dicarboxamide, 6-methyllumazine, N-{-*p*-[(2,4-dihydroxy-6-pteridylmethyl) methylamino]-benzoyl}-glutamic acid.

New syntheses of 2-methylquinoxaline and 1,2-diaminosuccinic acid were developed in connection with the proceding reaction sequence. 2-Methylquinoxaline was obtained by reduction of N-[(2-quinoxalyl) methyl]-pyridinium iodide formed from *o*-phenylenediamine and N-(2-formyl-2-bromoethyl)-pyridinium bromide. 1,2-Diaminosuccinic acid was prepared by iodine coupling of ethyl acetamidomalonate and acid hydrolysis of the coupling product.

p-[(2,4-Dihydroxy-6-pteridylmethyl) methylamino]-benzoic acid was obtained from 4,5-diamino-2,6-dihydroxypyrimidine sulfate, 2,3-dibromopropionaldehyde, and *p*-methylaminobenzoic acid.

N^4-[(2,4-Dihydroxy-6-pteridylmethyl) methylamino]-benzenesulfonamide and N^4-[(2,4-diamino-6-pteridylmethyl) methylamino]-benzenesulfonamide were prepared by condensation of 2,3-dibromopropionaldehyde and N^4-methylsulfanilamide with 4,5-diamino-2,6-dihydroxypyrimidine sulfate sulfate and 2,4,5,6-tetraaminopyrimidine sulfate, respectively.

Of the above six analogs, three were obtained in a pure state. The purified compounds were *p*-[(2,4-diamino-6-pteridylmethyl) methylamino]-benzoic acid, N^4-[(2,4-dihy-

droxy-6-pteridylmethyl) methylamino]-benzenesulfonamide. The other analogs were obtained as concentrates which were sufficiently pure for biological testing.

Studies were carried out in the synthesis of various β-(2-quinoxalyl)-propionaldehyde derivatives. The reaction of furfural with *o*-phenylenediamine did not yield the expected Schiff base. The amine exchange of *o*-phenylenediamine with 1-phenylimino-2-hydroxy-5-phenylamino-2,4-pentadiene hydrochloride was accomplished although the Schiff base could not be isolated. In the course of this study, N-2-furfurylidenemesidine was synthesized from furfural and mesidine, but acid hydrolysis failed to convert it to ethyl δ-mesidinolevulinate.

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VITA

The author was born on June 27, 1923, in Chicago, Illinois. He attended the public schools of Chicago, Illinois, and was graduated from Roosevelt High School in June, 1940. From September, 1940, to June, 1942, he attended Wright Junior College, Chicago, Illinois. In the fall of 1942 he entered Roosevelt College and was in attendance there until he enlisted in the Army of the United States in June, 1943. The author served in the American and European Theaters and was discharged in November, 1945. He reentered Roosevelt College in February, 1946, and received the Bachelor of Science degree in June, 1946. In September of that year he enrolled in the Graduate College of the University of Illinois, and was granted the degree of Master of Science in October, 1947. He held a part-time teaching assistantship from September, 1947, to June, 1950.